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# Radiotherapy and Hyperthermia

**D. González González, J.D.P. van Dijk and L.E.C.M. Blank**

**72 patients with either unresectable or pelvic recurrence of colorectal cancer were treated with combined radiotherapy and locoregional hyperthermia. Radiation doses were 50 Gy or more in patients not previously treated with radiotherapy, and 32 Gy (8 × 4 Gy) in patients who had previously received radiotherapy. Hyperthermia was administered within 30 min of irradiation, and the aim was to give four to six sessions once or twice a week, intending to reach temperatures of at least 41°C over 30 min. The mean of all the minimum (TMIN), maximum (TMAX) and median (TMED) intratumoral temperatures were 39.6, 41.1 and 40.2°C, respectively. Toxicity during hyperthermia treatment consisted mainly of local pain within the heated field (33%) and general discomfort (17%). In 17% of the patients, the hyperthermic treatment was prematurely stopped. Palliation was achieved in 75% of patients with a mean duration of 12 months. The percentage of palliated patients was higher when higher radiation doses were administered. No correlation between palliative effect and thermal parameters was found. A computed tomography scan proved objective remission was obtained in 11 patients (15%). Median survival was 11 months, and 17% of the patients were alive at 3 years. The literature on combined radiotherapy and hyperthermia in colorectal cancer is reviewed. From this review and our own data, it is concluded that thermoradiotherapy is feasible. Acute and late toxicity are not major problems, although pain and general discomfort hamper hyperthermic treatment. The most disappointing fact is that, with the available hyperthermia equipment, the increase in intratumoral temperature does not reach, in general, the therapeutic range.**

**Key words: colorectal cancer, radiotherapy, hyperthermia**
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## INTRODUCTION

APPROXIMATELY 15% of patients with colorectal cancer have inoperable tumours at presentation, technically unresectable tumours during laparotomy or tumours which are only resectable for palliation [1, 2]. Furthermore, tumours beyond the bowel wall, with or without positive lymph nodes (stages B2, C1, C2), have a high risk of local relapse of between 22 and 70% for rectal cancer and 14 and 41% for colon cancer, respectively [3–6]. If local recurrence does occur or if the tumour is unresectable, for the majority of the patients no effective curative therapy is available and only long-term palliation is considered. In patients with isolated locoregional relapse of rectal cancer treated with radiotherapy, the overall survival at 3 years is 10–13% [7, 8]. Duration of palliation has been reported to be approximately 3–6 months [9, 10]. In several studies, combined radio- and chemotherapy have been reported to improve symptomatic control and mean survival in patients with unresectable large bowel cancer [11, 12], but results from prospective studies have been negative [13, 14].

It is obvious from these data that, in spite of the considerable advances in the curative treatment of colorectal carcinoma, there is still room for improvement, both locoregional control and overall survival. The need for new therapeutic strategies for either cure or palliation is even more urgent in patients with unresectable tumours at presentation or relapsing after standard treatment.

The biological rationale for using hyperthermia in combination with radiation is based on two mechanisms, namely direct hyperthermic cytotoxicity against radioresistant cells and hyperthermic radiosensitisation [15]. The combination of hyperthermia and radiation, used either pre- or postoperatively, in the curative treatment of colorectal cancer is attractive because local control rates could be improved. Furthermore, unresectable tumours may become resectable with this combination compared with radiation alone. Finally, local palliative treatment of colorectal tumours remains difficult, and results with radiation alone, although well recognised, are far from optimal. We shall discuss below our experience in a group of patients with either primary unresectable or recurrent rectal carcinoma.

## PATIENTS AND METHODS

From 1985 to 1992, 72 patients with either pelvic recurrences of colorectal cancer or unresectable tumours were treated with combined radiotherapy and hyperthermia. All patients had deep-seated tumours histologically confirmed. Patients with recurrences in the abdominal wall or perineum, with cardiovascular disorders and with hip metallic prosthesis were excluded from the study. In 27 patients, relapse occurred following surgery without postoperative radiotherapy, another 27 patients had received irradiation, either postoperatively or at the moment of first relapse, and 18 patients were unresectable at presentation. The disease was locoregional in 49 patients and locoregional combined with distant metastases in 23 patients.

Correspondence to D. González González.
The authors are at the Department of Radiotherapy, Academic Medical Centre, University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam Zuidoost, The Netherlands.

Radiotherapy was administered with megavoltage equipment, and a box radiation technique was generally used. In patients previously irradiated or in poor general condition, the radiation schedule consisted of six to eight fractions of 4 Gy twice a week up to a total dose of 24–32 Gy (mean 31 Gy). In the group without previous irradiation, the planned dose was 50 Gy, five fractions per week (mean 49 Gy). Patients with unresectable tumours received 60–66 Gy in 6–7 weeks, five fractions per week (mean 59 Gy). Shrinking of the irradiation fields was performed after 40–45 Gy.

Hyperthermia was applied using a four-antennae array (Matched Phased Array) operating at 70 MHz [16]. One or two intratumoral catheters with closed ends were inserted for thermometry purposes. Thermocouple probes with five to seven sensors per probe were introduced into the catheters for monitoring temperatures during treatment. Additional probes were placed in the bladder, vagina, rectum lumen (in case of low anterior resection) and skin for estimation of the temperatures in normal tissues. The aim was to give four to six hyperthermia sessions, one or twice a week, to reach temperatures above 41°C for at least 30 min. Hyperthermia was given within 30 min of irradiation.

Main end-points of this phase I/II study were to determine what temperatures were reached with the available hyperthermia machine, tolerance during hyperthermia, toxicity attributed to hyperthermia and palliative effect. Objective response rate was evaluated by comparing preoperative computed tomography (CT) scan to CT scan done 3 months after the end of treatment. Patients were followed at 3-month intervals. All patients were informed of the experimental character of the hyperthermic treatment.

## RESULTS

A total of 292 hyperthermia treatments were applied with a mean of four sessions per patient. A summary of the thermal parameters is shown in Table 1. The means of all the minimum (TMIN), maximum (TMAX) and median (TMED) temperatures were 39.6°C, (±0.92), 41.1°C (±1.57) and 40.2°C (±1.02), respectively. It is clear from these results that in only a relatively small proportion of patients were intratumoral temperatures above what is considered the therapeutic range. This is also true when the percentage of sensors (T20:20%, T50:50%, T90:90%) at a given index temperature was estimated, i.e. in only 17% of the sessions were 90% of the temperature sensors above 40°C. The average number of minutes per session at a minimum temperature of 42°C (AVTMIN 42°C) was 1.1 (±2.5 S.D.) and at a maximum temperature of 42°C (AVTMAX 42°C) was 15.9 (±11.78 S.D.). As the mean number of sessions per patient was four, the cumulative number of minutes at a maximum temperature of 42°C within the tumour was 80.

Local pain within the heated field and general discomfort were observed in 33 and 17% of the patients, respectively, and in 17% of the sessions treatment was discontinued. In 29% of patients, the heart rate increased above 90 beats a minute. Although a light increase of the systolic and diastolic pressure occurred in the majority of the patients in only one session, the treatment was interrupted because of it.

The palliative effect is presented in Table 2. Good palliation was achieved in approximately 75% of the patients with a mean duration of 12 months. The percentage of palliated patients was higher when higher radiation doses were administered. No correlation between palliative effect and thermal parameters was found. A confirmed objective remission was obtained in 11 patients (15%), three complete remissions (CR) and eight partial responses (PR), respectively. The three CRs were achieved in patients with unresectable carcinomas who received a radiation dose of 66 Gy. These 3 patients were reoperated on and the pathological specimens did not show viable tumour cells. We could not demonstrate any correlation of objective remission with thermal parameters. Median survival (actuarial) was 11 months and 17% of the patients were alive at 3 years.

*Table 1. Thermal parameters in 72 patients with colorectal recurrences*

| | Temperature (°C) | No. of patients (%) | Mean ± S.D. |
|---|---|---|---|
| TMIN | 38.0–39.0 | 23 (32) | |
| | 39.1–40.0 | 31 (43) | |
| | 40.1–41.0 | 16 (22) | |
| | >41.0 | 2 (3) | 39.6 ± 0.92 |
| TMAX | 38.0–39.0 | 6 (8) | |
| | 39.1–40.0 | 11 (15) | |
| | 40.1–41.0 | 20 (28) | |
| | 41.1–42.0 | 21 (29) | |
| | >42.0 | 14 (19) | 41.1 ± 1.57 |
| TMED | 38.0–39.0 | 30 (43) | |
| | 39.1–40.0 | 18 (26) | |
| | 40.1–41.0 | 11 (16) | |
| | 41.1–42.0 | 11 (16) | |
| | Unknown | 2 (3) | 40.2 ± 1.02 |
| T20* | 38.6–39.0 | 3 (7) | |
| | 39.1–40.0 | 9 (22) | |
| | 40.1–41.0 | 15 (37) | |
| | 41.1–42.0 | 9 (22) | |
| | >42.0 | 5 (12) | 40.6 ± 1.11 |
| T50* | 38.4–39.0 | 6 (15) | |
| | 39.1–40.0 | 19 (46) | |
| | 40.1–41.0 | 10 (24) | |
| | 41.1–42.0 | 6 (15) | 40.0 ± 0.96 |
| T90* | 37.8–39.0 | 17 (41) | |
| | 39.1–40.0 | 17 (41) | |
| | 40.1–41.0 | 7 (17) | 39.2 ± 0.84 |
| AVTMIN42°C* | 0–5 | 35 (86) | |
| | >5 | 6 (14) | 1.1 ± 2.55 (min) |
| AVTMAX42°C* | 0–20 | 23 (56) | |
| | 21–30 | 14 (35) | |
| | >30 | 4 (9) | 15.9 ± 11.78 min |

*Estimated in only 41 patients.

## DISCUSSION

In general, the results obtained in the present study are in agreement with other published reports. During the course of the hyperthermic treatment, local pain within or around the heated field was relatively frequent (33% of patients), and it was the most important limiting factor in delivering hyperthermia. As a consequence of pain, power reduction and not infrequently discontinuation of treatment were necessary. General discomfort also contributed to a suboptimal delivery of the hyperthermic treatment. Similar results have been reported in other studies with locoregional deep-body hyperthermia [17–20]. Tachycardia, as well as an increase of the systolic and diastolic blood pressure, is frequently observed during hyperthermia but it has never resulted in discontinuation of treatment. However,

*Table 2. Palliative effect of thermoradiotherapy in 72 colorectal recurrences*

| | Before (%) | % at 3 months |
|---|---|---|
| Pain character | | |
| No pain/sporadic | 29 | 69 |
| Moderate | 20 | 16 |
| Severe | 51 | 15 |
| Pain medication | | |
| None/sporadic | 29 | 65 |
| Non-narcotics | 33 | 19 |
| Narcotics | 38 | 26 |
| Medication frequency | | |
| None/sporadic | 22 | 62 |
| 4–6 h | 32 | 17 |
| 1–3 h | 46 | 21 |
| Tenesmi | | |
| No | 63 | 82 |
| Yes | 37 | 18 |
| Discharges | | |
| No | 64 | 93 |
| Yes | 36 | 7 |
| Bleeding | | |
| No | 72 | 94 |
| Yes | 28 | 6 |

Mean duration of palliation 12.1 ± 11.5 months

*Table 3. Toxicity of locoregional thermoradiotherapy in abdomino-pelvic tumours (the majority colorectal)*

| | Reference | | | | |
|---|---|---|---|---|---|
| | 17 | 18 | 20 | 19 | Current trial |
| Local pain in heated field | 68% | 37%* | 50% | 35% | 33% |
| General discomfort | 23% | 32%* | — | 3% | 17% |
| Tachycardia | 13% | 35%* | — | 3% | 29% |
| Thermal blister | 2% | 5% | 0% | 3% | 0% |
| Infection catheters | 7% | 8% | 16% | 1% | 10% |
| % treatments stopped | 68% | — | — | — | 17% |
| Systemic temperature >39°C | — | 3%* | — | — | — |
| Fat/muscle necrosis | — | 5% | 6% | — | 0% |
| Obstructive ileus | — | — | 23% | — | 0% |
| Intestinal fistula | — | — | 10% | — | 0% |
| Intestinal perforation | — | — | 6% | — | 0% |
| Bladder bleeding | — | — | 0% | — | 0% |
| Hydronephrosis | — | — | — | — | 3% |
| Lost catheter | — | — | — | — | 1% |

*Percentage of sessions where a given toxicity was registered.

patients with serious cardiovascular problems must not be entered in studies where deep-body hyperthermia is used. We did not observe fatty necrosis in our study on colorectal cancer, but in a series of 15 patients with cervical carcinoma, fat necrosis occurred in 3 patients, who were extremely obese. A case of severe myonecrosis and 2 cases of myonecrosis and peripheral neuropathy following deep regional hyperthermia have also been reported [21, 22]. In 10% of our patients, infection around the catheters for thermometry occurred and this problem has also been found by others [17–20, 23]. Acute toxicity including nausea, vomiting, diarrhoea and abdominal cramps was similar to that with radiation alone. The only late toxicity observed was hydronephrosis in 2 patients. These patients had unresectable rectal cancer at first laparotomy. After a dose of 66 Gy and six hyperthermia sessions, a second laparotomy was performed and the tumour could be radically resected. 6 and 9 months after the second operation, bilateral hydronephrosis occurred, treated in 1 case with ureter deviation and in the other with a retrograde drain. Although hyperthermic treatment could have contributed to this complication, high radiation dose and two surgical procedures could also be the cause of this problem. A summary of the more relevant toxicities observed by different authors is presented in Table 3.

The most disappointing result of our study was the difficulty in heating substantial areas of the tumour to a temperature considered to be cytotoxic (>42°C). Pain and general discomfort limited the duration of treatment and hampered optimal power usage. Similar problems have been reported in the studies where electromagnetic deep-body hyperthermia has been applied [17–20]. In order to reach higher and homogeneous intratumoral temperatures, a better and more selective targeting of the power is necessary. Hyperthermia three-dimensional planning systems are now being developed which could help optimise heat distribution in tumoral and normal tissues. Alternatively, new technological approaches, such as the use of scanned focused ultrasound hyperthermia and interstitial hyperthermia, are potential methods of improving selective heating of tumours.

The palliative effect of the combined treatment was important. Pain, tenesmi, discharges and bleeding either disappeared or diminished in more than 40% of the patients who had these symptoms. The mean duration of the palliative effect was 12 months, which is longer than that reported for a similar group of patients treated with radiation alone [9, 10]. Notably, pain relief was obtained in 78% of the patients. Pain relief reported in other series is summarised in Table 4. The palliative effect was better when higher radiation doses were administered, but there was no correlation with thermal parameters. The same results were found in other studies with deep-body hyperthermia [18, 19, 24].

In pelvic recurrences of colorectal cancer, evaluation of objective response is difficult and CT scan and magnetic resonance imaging (MRI) are generally used. When strict criteria (50% or more reduction of the initial maximum diameter for PR and complete tumour disappearance for CR) were followed, we only obtained 15% objective response. This result is lower than in other series as shown in Table 5. Reasons for these differences could be the use of lower radiation doses in patients who had previously received radiotherapy, less effective hyperthermia in our series, and perhaps adherence to strict criteria for the definition of response.

The overall survival at 3 years was 17%, which is comparable

*Table 4. Pain relief with thermoradiotherapy in pelvic tumours*

| Reference | No. of patients | Pain relief CP(%) | PP(%) | CP + PP(%) |
|---|---|---|---|---|
| Feldmann *et al.* [18] | 32 | 47 | 31 | 78 |
| Kakehi *et al.* [24] | 34 | — | — | 56 |
| Berdov *et al.* [25] | 48 | — | — | 86 |
| Petrovich *et al.* [19] | 195 | 23 | 39 | 62 |
| Current trial | 69 | 42 | 37 | 79 |

CP, complete palliation; PP, partial palliation.

*Table 5. Objective response rate in colorectal cancer treated with thermoradiotherapy*

| Reference | No. of patients | CR | | PR | | CR+PR | | Comments |
|---|---|---|---|---|---|---|---|---|
| | | RT | RT+HT | RT | RT+HT | RT | RT+HT | |
| Feldmann *et al.* [18] | 36 | — | 2 | — | 9 | — | 11 (31%) | Colorectal: 18 rec., 1 adv. |
| Nishimura *et al.* [20] | 71 | 2/36 | 4/35 | 8/36 | 15/35 | 10 (27%) | 19 (54%) | 62 rec., 9 adv. |
| Emami *et al.* [17] | 44 | — | 17 | — | 6 | — | 23 (52%) | Pelvis, abdomen, 44% adenocarcinoma |
| Berdov *et al.* [25] | 115 | 1/59 | 9/56 | 20/59 | 30/56 | 21 (36%) | 39 (70%) | Rectal, randomised study |
| Kakehi *et al.* [24] | 43 | — | 2 | — | 23 | — | 25 (58%) | Rectal, 34 rec., 9 preop. |
| Petrovich *et al.* [19] | 196 | — | 18 | — | 33 | — | 51 (26%) | Pelvic tumours |
| Current trial | 72 | — | 3 | — | 8 | — | 11 (15%) | Colorectal, 36% SD |

adv, advanced; rec, recurrence; preop, preoperative; CR, complete remission; PR, partial response; RT, radiation treatment; HT, heat treatment.

to other reported series [7, 8]. Thus far, two randomised studies in advanced rectal cancer have been reported [25–27]. Preoperative radiotherapy alone was compared to preoperative thermoradiotherapy. In both studies, the percentage of resected patients, objective response rate, freedom of pelvic recurrence and long-term overall survival were significantly better in the group of patients randomised to receive thermoradiotherapy. In these two studies, hyperthermia was applied intrarectally and tumour temperatures were not registered. Further, the number of patients entered in the studies was relatively small.

From our results and the reviewed data, it is not possible to make definitive conclusions on the value of hyperthermia in the treatment of colorectal cancer. The results of several phase I/II studies seem to indicate that thermoradiotherapy is feasible, and that acute and late toxicity are not major problems. However, in practically all the studies, pain and discomfort hampered hyperthermic treatment in a large proportion of patients, and resulted in interrupted or discontinued treatment or patient refusal. The objective remission rate has been approximately 45% (range 1–70%) and palliation has been achieved in more than 60% of patients. The most disappointing fact is that, with the available hyperthermia equipment, the increase in intratumoral temperature did not reach, in general, the therapeutic range, i.e. >42°C for at least 30 min. However, it is possible that temperatures in the range of 40–41°C could have some direct cytotoxic effect, and could also homogenise blood flow in the tumour so increasing radiosensitivity. Prospective randomised studies must be performed before the role of hyperthermia in the management of cancer, in general, and of cancer of the lower gastrointestinal tract in particular is established.


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